Annual report : 1994 / Gene Therapy Advisory Committee.

GENE THERAPY ADVISORY COMMITTEE

FIRST ANNUAL REPORT

NOVEMBER 1993 – DECEMBER 1994

Health Departments of the United Kingdom
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This report covers the period from the appointment of the Gene Therapy Advisory Committee in November 1993 to 31 December 1994.

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FOREWORD

In his Foreword to the Report of the Committee on the Ethics of Gene Therapy, Sir Cecil Clothier emphasised the importance of not seeking to prohibit the progress of science but, at the same time, to guide its application. A central recommendation of that Committee was that a supervisory Committee should be established to keep an acceptable balance between these principles. The new Committee, the Gene Therapy Advisory Committee, was formed in 1993, and we have striven over our first year to follow his precepts. This is our first report.

The timing of our birth was opportune. Clinical trials of gene therapy in the UK were just beginning. The Clothier Committee had done some developmental work and we have built on those foundations. Our experience during the year has confirmed the wisdom of the recommendation that we should be set up in the first place as a non-statutory body. This has allowed us flexibility in our approach to our work and to the growing number and diversity of applications which have been submitted.

Knowledge about the current status of gene therapy in the UK and the workings of the Committee should be widely disseminated. Our meetings are held in private, and we take great care to safeguard confidentiality and privacy of patients and their families, but our method of working, and our conclusions and recommendations are made widely known. This report is an important opportunity to inform all who wish to know what gene therapy research has been approved in the past year and to make a difficult subject understandable. It needs to be emphasised, however, that approval by GTAC does not necessarily mean that research work has started; the actual gene preparation has to be made and agreement obtained from the Medicines Control Agency for its use; and patients have to be recruited. In our next report we hope to be able to comment on more studies that are in progress, with the assurance that the highest ethical standards are being maintained.

It was widely anticipated that children with inherited disease would be among the first candidates for gene therapy. In the event this has been the case only in a single instance and for a very rare condition. There has also been only one common inherited disease, cystic fibrosis, in which an attempt is being made in the UK to explore the use of gene therapy. The majority of trials proposed so far, both in the UK and the US, have concerned the alleviation of various forms of cancer, by using genes to enhance the response of the immune system or to make the body more susceptible to certain drugs.

In the future we can expect trials for a wider range of diseases, but the application of gene therapy in any routine sense for health care is a long way off. A prolonged period of research lies ahead and it would be wrong to expect immediate returns or instant cures in view of the time and effort that must be expended.

A major duty of GTAC is to consider the ethical acceptability of proposals for gene therapy research. In doing so, it in no way usurps the responsibilities of Local Research Ethics Committees; rather it seeks to support, strengthen, and supplement their activities. Ethical review includes appraisal of the scientific merit of the work in a new and complex field which is rapidly developing. GTAC's medical and scientific members are helped by advisors who review proposals relevant to their expertise. The - for want of a better term - "lay" members of the Committee keep everyone's feet on the ground and ensure that all aspects of the research are rigorously examined from the patient's point of view. I am immensely grateful to them all.

This Foreword would not be complete without acknowledgment of the hard work of the small secretariat which supports the Committee. Both Committee members and proposers owe a great deal to their expertise.

Professor Dame June Lloyd
January 1995

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SECTION 1 - INTRODUCTION

BACKGROUND TO GENE THERAPY IN THE UK

1.1 *Gene therapy** is one of the more recent areas for the application of *molecular biology* to the field of human health. In the UK, the Government set up the Committee on the Ethics of Gene Therapy, under the chairmanship of Sir Cecil Clothier, in 1989. Its task was to draw up ethical guidance for the medical profession on treatment of *genetic disorders* in adults and children by genetic modification of human body cells.

1.2 In the USA, the National Institutes of Health Recombinant DNA Advisory Committee (RAC) published the first guidance " Points to consider in the design and submission of human *somatic cell* gene therapy protocols" in 1989[1]. It was under a draft of these guidelines that the first protocol for gene therapy had been reviewed in the previous year.

1.3 In 1988, the European Medical Research Councils (EMRCs) of 11 Western European nations, including the UK, produced a joint statement calling for a coordinated approach to the development of molecular biology which would be applied to human therapeutic interventions, including gene therapy.

1.4 In their statement the EMRCs recommended:

(a) that gene therapy should be limited to interventions aimed at correcting disease or defects.

(b) that it should be limited to somatic cells.

(c) that research be aimed at the development of safe species and tissue specific *vectors* for gene delivery.

They concluded:

(d) that gene therapy raises only familiar ethical issues.

(e) and that there was a need to agree national guidelines for good practice and to establish national bodies to oversee clinical trials.

1.5 The Clothier Committee's task was to draw up ethical guidance for the medical profession on treatment of genetic disorders by genetic modification of human body cells; to invite and give ethical considerations to proposals from doctors wishing to use such treatment on individual patients; and to provide advice to UK Health Ministers on scientific and medical developments which had a bearing on the safety and efficacy of human gene modification.

1.6 The Clothier Committee invited the submission of evidence during 1990 and its detailed report was finalised in 1991[2]. This report provided the ground rules under which gene therapy has moved ahead in the UK over the last two years.

1.7 First, in terms of ethical issues, Clothier concluded that gene therapy should not be considered as ordinary medical practice, but that it should be regarded, at least initially, as research involving human subjects and therefore that it should be controlled by standards that were at least as exacting as those already applying to other medical research. Clothier drew attention to the accepted ethical codes whose purposes are to:

(a) facilitate justifiable advancement of biomedical knowledge;

(b) maintain ethical standards of practice;

(c) protect the subjects of research from harm;

(d) preserve subjects' rights and liberties; and

(e) provide reassurance to the public, to the professions and to Parliament that these are being done.

1.8 The report recommended that gene therapy should be subject to approval only after authoritative ethical review, including consideration of its medical and scientific merit, the legal implications, and wider public concerns.

*Because it has been necessary to use some technical terms in describing the protocols, a glossary is appended to describe these. Words appearing in the glossary are italicised the first time they appear in the text.

1.9 Within the UK there is an established system of local research ethics committees (LRECs) which carry out such a review function. A LREC must be consulted about any research proposal involving NHS patients, their records, use of NHS premises etc. Following consultation with LRECs, the Clothier Committee concluded that gene therapy research raised issues that would be beyond the technical competence of many LRECs, and therefore recommended that a national supervisory body should be established to consider and advise on the acceptability of protocols in this specific area of medical research. This body would, however, complement LRECs and not usurp their local function.

1.10 The next ground rule was that, in the present state of knowledge, no attempt to intervene in *germ line cells* should be made.

1.11 Finally, gene therapy research should remain restricted to disorders that are life threatening or cause serious handicap and for which treatment is either unavailable or unsatisfactory.

ESTABLISHMENT OF GTAC

1.12 Following wide consultation on the Clothier report, Health Ministers accepted the recommendations in principle. During 1993 Ministers set out the terms of reference and membership of the new body to succeed the Clothier Committee. Until the new body was in place, the Clothier Committee was asked to operate transitional arrangements for the review of those protocols that were submitted to it during the interim period.

1.13 In any rapidly evolving field, it is important to maintain a system of review that is sufficiently flexible to respond to the foreseeable developments in research and clinical practice. GTAC was established by Government on a non-statutory basis, although it has been made clear to all those with responsibility for gene therapy research that no study involving human subjects should proceed without prior review by both GTAC and a local research ethics committee.

1.14 The Clothier Committee believed that although somatic gene therapy raised no new ethical dilemmas, it was clear from the consultation responses to the report that the public, professions and Parliament all wanted a national system of ethical oversight established that could be seen to be conducted in a way that was beyond reproach.

1.15 The Gene Therapy Advisory Committee (GTAC) held its first meeting in November 1993. The Committee has three main functions: (a) carrying out a case-by-case review of individual protocols; (b) reviewing more general issues relating to such therapy and (c) providing advice to UK Health Ministers on developments in this field and on their implications. (See Annex 1)

1.16 The Committee was constituted with a broad membership intended to provide confidence to all concerned with any aspect of gene therapy research. About one half of the members bring scientific and medical skills, and half bring experience from backgrounds in genetic counselling, ethics, nursing, law, psychology, hospital management, industry, the media and medical charities. (See Annex 2)

1.17 During the transitional arrangements for review of proposals to conduct gene therapy research the Clothier Committee was strengthened by having access to advice provided by a group of experts who acted as referees. The experience gained during that period led to that group being asked to continue in place to assist GTAC. (See Annex 3)

1.18 As well as working closely with the appropriate LRECs, GTAC works with the Medicines Control Agency (MCA) who have statutory responsibility for all clinical trials under the Medicines Act. MCA staff sit as observers on GTAC to ensure close liaison is maintained. The GTAC Secretariat also maintains links with the Advisory Committee on Genetic Modification (ACGM) at the Health and Safety Executive in respect of legislation dealing with the contained use of genetically modified organisms. (See Annex 4)

METHOD OF WORKING

1.19 When a protocol for gene therapy research is submitted to GTAC, it is essential that sufficient time is allowed for the Committee to seek further information about protocols where appro-

priate before it meets to discuss the proposal. Thus, GTAC encourages researchers to make early contact with its Secretariat to discuss the proposed work. The Secretariat carries out an initial review of the protocol to ensure that it addresses all relevant points, seeking clarification as necessary. When the protocol is complete it is sent to appropriate members of GTAC's group of experts, for confidential review.

1.20 The views of the referees are presented to both the proposers and GTAC and are discussed by the Committee. GTAC finds it extremely valuable to have the researchers present during the review by the Committee to provide additional information and to answer the Committee's outstanding questions.

1.21 All decisions by GTAC are conditional upon the proposals obtaining the appropriate permissions from their local research ethics committee and from the Medicines Control Agency in respect of the requirements of the Medicines Act.

1.22 Experience has shown that a submission to GTAC should be made at least 90 days before the anticipated date of review by the Committee in order that the review process described above can take place. The actual meeting at which GTAC will review a protocol will be confirmed by the Secretariat once any additional information sought from the proposers has been received.

1.23 GTAC has four more meetings planned for 1995. The dates are:

11 May
20 July
5 October
13 December.

SECTION 2 - PROTOCOLS* CONSIDERED BY GTAC IN 1993/94

2.1 GTAC met for the first time in November 1993, and during 1994 held a further five meetings. In many ways, this first year has been a learning experience, both for the Committee and for the researchers who have come to its meetings to present their research protocols.

2.2 By December 1994, GTAC (and its predecessor the Committee on the Ethics of Gene Therapy) had received a total of twelve protocols for review and was content in principle, subject to conditions, for ten protocols for gene therapy research in human subjects to proceed. The remaining two protocols were still under consideration at the time of this report.

2.3 Protocols on which GTAC has completed its review include studies in the following diseases: severe combined immunodeficiency (1), cystic fibrosis (4), malignant melanoma (2), lymphoma (2) and neuroblastoma (1). Protocols have also been submitted for studies in breast cancer and acute myeloid leukaemia.

SEVERE COMBINED IMMUNODEFICIENCY SYNDROME

2.4 Severe Combined Immunodeficiency (SCID) is a rare form of inherited disorder in which the immune system is progressively damaged as a result of a defective *gene*, which in healthy individuals produces the *enzyme* adenosine deaminase (ADA). SCID due to *ADA deficiency* arises in a very small number of infants (approximately 5 per year in the UK). The disease was one of the first targets for gene therapy in the USA, two children undergoing gene therapy in 1990.

Adenosine deaminase (ADA) gene transfer in a child with severe combined immunodeficiency syndrome - Institute of Child Health/ Hospitals for Sick Children, Great Ormond Street, London.

In January 1993, the Committee on the Ethics of Gene Therapy approved a protocol in which a patient with ADA deficiency was to be treated by gene therapy. Bone marrow cells were removed, grown in the laboratory and then modified with a *retrovirus* carrying the normal human ADA gene. The bone marrow cells were then returned to the child. This research trial was carried out in March 1993.

In a report back to GTAC in July 1994, the research team reported that although evidence of the gene had been found in bone marrow at six months post therapy, it was not possible to detect the gene on analysis at one year after the transplant. The patient remained in good health on treatment with PEG-ADA, a drug used to manage ADA deficiency, and will continue to be monitored for ADA gene activity and for any side effects of the therapy. Although there are no plans to repeat the gene therapy in this patient, in the view of the researchers, the technique remains an option for the treatment of ADA deficiency.

CYSTIC FIBROSIS

2.5 Cystic Fibrosis (CF) is one of the most common inherited serious genetic diseases in the UK, affecting nearly 7,000 patients, with approximately 300 new cases per year. The secretion of mucus by the membranes which line the airways, the gut and the ducts of glands is abnormally sticky and the consequences are progressive lung damage, impaired digestion and nutrition, and failure to thrive. Affected males are infertile. Although advances in treatment and care have improved both survival and the quality of life, the long term prognosis remains poor, and few patients survive beyond middle age.

2.6 In healthy individuals, a gene (often called the CF gene) expresses a protein called *cystic fibrosis transmembrane conductance regulator (CFTR)*. The absence of or a defect in the normal gene is associated with the disease. Since the identification and isolation of the CF gene in 1989, efforts have concentrated on developing techniques for gene therapy to make good the defective production of CFTR in the organs most affected.

*A summary of all the gene therapy protocols approved by GTAC is to be found at Annex 5.

(a) Gene Therapy Research for Cystic Fibrosis - Royal Brompton National Heart and Lung Hospital/St Mary's Hospital Medical School, London.

Prior to the establishment of GTAC, the Clothier Committee considered an application for an initial trial to test one mechanism for gene delivery. This involved the delivery of the human CF gene into the noses of 12 male patients with cystic fibrosis. The gene delivery system chosen was to be a *cationic liposome*. Liposomes can fuse with cell membranes and thereby deliver DNA, in this case the CF gene, into the cell cytoplasm. The Clothier Committee was content with the protocol and the study commenced in September 1993.

In February 1994, GTAC agreed to extend the trial to a further 3 patients. A request to allow recruitment of female patients, who may be fertile, was agreed in March 1994 following the submission of supporting safety data to address the Committee's concern over possible gene transfer to germ cells. The results of this initial research trial were presented to GTAC in July 1994.

A specific gene product was detected in 5 out of the 9 patients receiving the CF-liposome complex (6 patients acted as controls). A restoration of 20% of the deficit in cell membrane chloride transport (a function of the gene) was seen which peaked at 3 days and lasted approximately 7 days after application of the liposomes[3].

(b) Towards gene therapy for cystic fibrosis - Institute of Molecular Medicine, Oxford/Wellcome/CRC Institute of Cancer and Developmental Biology, Cambridge and University of Cambridge.

This represented the second trial which proposed the delivery of the CF gene into the nasal epithelium of CF patients using a liposome - DNA delivery system.

The protocol formed part of a longer term study to deliver the CF gene to the lungs of CF patients. GTAC wished to see this programme of work progress in a stepwise fashion, and considered only the nasal phase of the study. This trial used the same liposome and gene as that used in trial (a), although the *plasmids* utilised differed from the trial at the Royal Brompton Hospital.

At its second meeting in February 1994, subject to provision of further data to support the belief that liposomal DNA would not express in other tissues, GTAC was content with the first two parts of the study; direct application of liposomal DNA to nasal polyps, and to the nasal epithelium.

(c) Gene Therapy for the treatment of Cystic Fibrosis - City Hospital/Western General Hospital, Edinburgh.

This proposal was the third in which GTAC was asked to review application of the CF gene to the nasal epithelium and lungs of CF patients.

As in the other UK proposals lipid complexes known as liposomes are to be used as vehicles to carry DNA into the cell. Liposomal DNA will be administered as single applications to the nasal cell membrane epithelium and to the lungs.

The earlier trials reviewed by GTAC used the lipid (DC-Chol/DOPE) and same gene (CF). In this trial:

(i) the proposers sought to use a CF gene construct with a different *promoter;*
(ii) Whilst an initial group of patients would receive the lipid DC-Chol/DOPE, the proposers sought approval to use a second lipid DOTAP, in a second group.

As in previous trials, GTAC declined to consider the lung stage of the work until the preliminary study in the nasal epithelium was carried out and the results reported to the Committee.

Subject to receipt of additional data to demonstrate lack of gene transfer to other tissues and the inclusion of use of effective contraception in the eligibility criteria for female participants in the trial to minimise the risk of germ-line

gene transfer, GTAC approved the protocol at its May 1994 meeting.

(d) Gene Therapy for Cystic Fibrosis: Protocol for Phase I studies - Royal Brompton Hospital/St Mary's Hospital, London.

This proposal was the second part of the research programme in cystic fibrosis patients at the Royal Brompton Hospital. The Clothier Committee had approved a nasal study in March 1993 (study (a) above).

In this application, the researchers reviewed the findings from their initial study in which they had demonstrated gene transfer and expression in some of their patients, and little or no indications of inflammation at the site of administration.

The protocol called for administration of the CF gene as liposomal DNA into the lungs of adult volunteers with mild cystic fibrosis lung disease, by a nebuliser. The protocol was reviewed by GTAC at its July 1994 meeting. Subject to receipt of toxicology data, modifications to the patient information leaflet, and amendments to the eligibility criteria, GTAC agreed the proposal.

MALIGNANT MELANOMA

2.7 Malignant melanoma is an increasingly common skin cancer from which 1,300 people in the UK now die each year. Although localised disease can be cured by surgery and two-thirds of the 3,500 new cases each year are successfully treated, patients with disseminated disease have a poor prognosis, 10% or less surviving for up to two years.

2.8 Developments in chemotherapy have not markedly improved survival in *metastatic* disease. There is however evidence that the body can mount an immune response against this disease and attention is being given to ways of enhancing such a response.

(a) Gene Therapy for metastatic melanoma: Assessment of expression of DNA constructs directly injected into metastases - ICRF Molecular Oncology Laboratory, Oxford.

In May 1993, prior to the establishment of GTAC, the Clothier Committee carried out an initial review of a proposal to conduct gene therapy research in patients with metastatic melanoma. In the light of discussion with the proposers, GTAC received an amended protocol for review at its third meeting in April 1994.

The essential feature of the proposal is the direct injection of a genetically modified DNA into a skin tumour. The aim is to demonstrate that expression of a marker gene will occur specifically at the site of a melanoma following the direct injection of a plasmid DNA preparation. If this is successful, the second stage will involve the replacement of the marker gene with that coding for Interleukin-2 (IL-2).

IL-2 is a *cytokine*, one of a family of soluble proteins which play an important role in the behaviour of cell populations. *Lymphocytes* exposed to IL-2 can kill tumour cells, and in animals can cause the regression of established liver and lung tumours.

Recombinant IL-2 has been available for some years and treatment of patients presenting with advanced cancers began in the mid 1980's. Although anti-tumour responses were observed, the short duration of effect of the protein along with the systemic toxicity of high doses of IL-2 have remained serious drawbacks. A number of gene therapy approaches have been employed in the USA to deliver cytokines such as IL-2 directly to tumour sites, which allows lower doses to be used.

In the proposed research, a group of patients with metastatic melanoma will be entered into the study. A DNA preparation containing a melanoma specific promoter and the E.coli gene, *B-galactosidase* (B-Gal) will be used. It will be administered locally to a melanoma site, usually in the skin. A series of tests on the melanomas, which will be removed after 1,2 or 3 weeks, will be used to assess whether marker gene expression has occurred. If this is suc-

cessful, patients will be given local administration of a plasmid DNA, again containing the melanoma specific promoter, but with the gene coding for IL-2 replacing the B-Gal marker.

GTAC agreed the study in May 1994, subject to modification to the patient assessment criteria, the inclusion of effective contraception in the trial eligibility criteria and amendments to the patient information letter.

(b) The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secrete interleukin-2; A Phase IB trial - Royal Marsden Hospital/Institute of Cancer Research, London.

In this study, cells from each patient's melanoma will be cultured in the laboratory. Each culture will be infected with a genetically modified retrovirus carrying the gene for interleukin 2 (IL-2).

The protocol calls for the recruitment of up to 12 patients presenting with histologically confirmed melanoma with evidence of metastatic spread. Such patients have a median survival of about 6 months. The patients will be immunised with their own melanoma cells which will have been grown in tissue culture and genetically modified to produce IL-2 from the IL-2 gene delivered via a retroviral vector. The cells will be irradiated to prevent further spread before being reintroduced to the patient by subcutaneous injection close to the site of either affected skin or lymph node(s).

The aim of this approach is to use the IL-2 secreting cells to stimulate an anti-tumour immune response in the patient. This early clinical research has the specific targets of (a) evaluating the biological effect of the "vaccine" and (b) providing basic toxicity data.

GTAC gave conditional approval to this study in February 1994 subject to the provision of appropriate safety data on the vector and packaging cell line. Final approval was given in August 1994 and the trial commenced in October 1994.

LYMPHOMA

2.9 The malignant lymphomas comprising Hodgkin's Disease (HD) and the Non-Hodgkins lymphomas (NHL) are among the commonest curable cancers. The introduction of combination chemotherapy has resulted in long term survival of approximately 70% and 35% of patients with HD and NHL respectively.

2.10 Follicular B-cell lymphoma, a form of NHL, is a slowly progressive malignant disease which, over a period of a few years, tends to become non-responsive to treatments such as chemotherapy and radiotherapy. Patients are usually diagnosed between 50 to 60 years of age and survive on average about 8 years.

A Pilot Study of Idiotypic Vaccination for Follicular B-cell Lymphoma using a Genetic Approach - MRC Cambridge Centre for Protein Engineering, Cambridge.

Because the disease has a tendency to wax and wane (without therapy) with frequent spontaneous regressions and even complete remissions, the proposers believe that it is normally under a degree of immunological restraint, albeit suboptimal.

The *immunoglobulin* expressed on the surface of the lymphoma *B cells* is unique to a given lymphoma, distinguishing it from the normal B cells of the patient and from the lymphomas of other patients. The proposers have identified and isolated the gene which codes for this immunoglobulin. They propose that this is incorporated in a vector (in this case a plasmid) which will be administered to the patient as an injection into muscle. The aim is that for each individual patient's lymphoma, the immunoglobulin genes will be expressed with production of the immunoglobulin which will then induce a specific anti tumour response. The hope is that the response will be sufficient to eradicate the tumour.

Following review at the Clothier Committee outline agreement was given for this proposal in July 1993, subject to further studies being carried out to demonstrate that the gene which was inserted was not taken up or

expressed in the germ line, and to the patient information being amended to provide a simple, non-technical explanation of the study. That additional information was presented to GTAC which agreed the protocol in December 1993.

Patients recruited into a phase I trial will be those patients who have relapsed or who have persistent disease after chemotherapy. The aim in this pilot study is to investigate dose-related toxicity to establish whether there is a safe dose of plasmid DNA which will ensure uptake and subsequent expression of the protein and elicit a specific immune response.

2.11 HD and NHL patients in whom conventional chemotherapy has failed may respond to very high dose treatment in which part of the patients own bone marrow stem cells are temporarily removed to spare it the toxicity that accompanies such intense drug therapy. High dose therapy is only effective in selective patients and some patients may still be at very high risk of relapse.

Transfer of the Human Multi-Drug Resistance Gene into the Haemopoietic Cells of Patients Undergoing High Dose Therapy and Autologous Stem Cells Transplantation for Malignant Lymphoma – University College Medical School, London.

At its December 1994 meeting GTAC considered a protocol in which the MDR-1 gene, which is responsible for cells becoming resistant to many of the drugs used in anti-cancer therapy, will be transferred to blood *stem cells*.

Blood stem progenitor cells will be taken from up to 9 patients and modified, using a retroviral vector, to carry the MDR gene.

The modified cells will be returned to patients in the belief that this will permit more effective high dose therapy of those at risk of relapse in HD and NHL. Higher doses of drug may be used in treatment whilst the MDR gene helps protect the normal cells of the haemopoetic system.

GTAC approved the proposed trial with conditions relating to the provision of data from related trials, amendment of the eligibility criteria and patient information sheets.

NEUROBLASTOMA

2.12 Neuroblastoma is a tumour of childhood which arises from nerve cells outside the brain. Affected children most often present with an abdominal mass and in 70% of cases the tumour has already spread. About 120 children per annum are affected in the UK and the outcome for those whose disease has spread is poor. Most do not survive 5 years despite intensive treatment.

Use of gene transfer to determine the role of tumour cells in bone marrow used for autologous transplantation and the efficiency of immunomagnetic "purging" the bone marrow - ICRF Paediatric and Neuro-Oncology Group, Frenchay Hospital, Bristol.

When patients enter remission following initial therapy of neuroblastoma, bone marrow can be harvested and stored. Further intensive therapy to remove any remaining microscopic amounts of disease also destroys the remaining bone marrow in the patient and they are then "rescued" by return of the bone marrow harvested and stored earlier. Such marrow might however contain tumour cells and it is the practice in some centres to try to remove such cells by specific *purging* techniques. However, except for one small unpublished study, it has not been shown that this reduces the risk of relapse compared with the return of "non-purged" cells.

The proposed method is to label bone marrow cells with genetic markers which could be detected in the tumour cells of children who relapse, thus showing whether the relapse originated in the returned marrow or from tumour remaining in the body.
Bone marrow cells will be exposed to two different retroviral vectors. Both vectors will carry the antibiotic marker gene for resistance to *neomycin* (neo). One will be used to mark cells which have been subjected to purging (a

technique which is intended to remove tumour cells selectively from the bone marrow), the other vector will be used to mark cells not so treated. The two portions of marrow will then be mixed and reintroduced into the patient.

Tumours in those patients who relapse will be assayed to determine; i) whether tumour cells from the returned marrow are responsible for relapse, and ii) to provide data on the efficiency of purging.

At its first meeting in November 1993, GTAC considered a gene transfer protocol in which children with Stage 4 neuroblastoma (those in whom the disease has spread and the outlook is very poor) would be recruited into the research trial. GTAC approved the trial, requesting that independent counselling should be offered to parents before their children were recruited into the programme.

PROTOCOLS STILL UNDER REVIEW AT THE END OF 1994

2.13 A further two proposed programmes of gene therapy research were submitted for GTAC review during the Committee's first year of work. The disease targets of these protocols are breast cancer and acute myeloid leukaemia. One has been reviewed and a decision deferred pending the supply of additional information. The other protocol is expected to be put to the Committee shortly.

GENERAL COMMENTS ON THE PROTOCOLS

2.14 The proposals have concerned new and difficult areas of science and each has raised new questions and new problems. It was, therefore, only to be expected that additional information would need to be sought in many cases by the Secretariat before Committee review could be completed. The Committee welcomed the way in which the proposers have co-operated both in the provision of such information and in readily discussing their protocols with the Committee.

2.15 GTAC will continue the practice of seeking advice as appropriate from its panel of expert advisers prior to consideration of protocols and will widen the membership as appropriate. The Committee wishes to record its thanks to the panel for their invaluable contribution to its work.

2.16 One specific area has been highlighted as a particular challenge for proposers and GTAC alike. The Committee has found it necessary in most cases to request improvements to the patient information leaflets. GTAC believes, as did the Clothier Committee, that patients are being invited to participate in research on the basis of full information and consent. It is therefore especially important when patients are suffering from serious or life-threatening diseases that the balance of the information provided is given particular attention. Many of these early gene therapy research trials are unlikely to benefit individual patients significantly and the importance of communicating the value of such trials whilst not raising false hopes in patients and their families, no matter how well meant, is a special challenge.

2.17 GTAC has found that information leaflets are often written with assumptions about technical knowledge and understanding of complex language that cannot reasonably be expected of the majority of patients. In order to assist proposers of research to deal with this issue, GTAC is currently completing guidance offering advice on what should be covered in patient information for gene therapy research. This will be available early in 1995.

SECTION 3 - GENE THERAPY: INTERNATIONAL DEVELOPMENTS

3.1 The first protocol for a gene therapy experiment on human subjects was reviewed by the Recombinant DNA Advisory Committee (RAC) of the US National Institutes of Health in 1988. This was for a gene marker experiment in patients with advanced cancer. By September 1994 a total of 81 protocols had been approved in the USA. The great majority of these trials are in the area of malignant disease, inherited single gene disorders such as cystic fibrosis or ADA deficiency accounting for only 15% of the submissions.

3.2 The US system of review is similar in structure to that developed in the United Kingdom: there is local ethical consideration (by Institutional Review Boards), assessment by a specialist national advisory committee (RAC) and licensing by the appropriate medicines authority.

3.3 1994 saw the first published reports of a small number of gene therapy trials[4,5]. Although clinical intervention may be some way off, early results are encouraging.

3.4 In Europe, France had six trials approved by April 1994, with two already underway, and gene therapy trials have also commenced in Italy, and in the Netherlands[6].

3.5 1994 has seen the first application to the Japanese Ministry of Health and Welfare for permission for a research trial in ADA deficiency. Further trials are known to be under consideration by local ethical committees in Japan.

SECTION 4 - OTHER GTAC ACTIVITIES - GUIDANCE NOTES

4.1 At the outset, the Committee recognised that uncertainty over what would be demanded of scientists and clinicians when making their submissions would be likely to lead to unacceptable delays. GTAC therefore set as one of its very first priorities the preparation of guidance for researchers.

4.2 Much has been learnt from the considerable work of the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health in the US. This, together with the experience gained with the first proposals seen by the Committee and its Secretariat, and discussion with medical scientists in this field, have greatly contributed to the development of the GTAC guidelines.

4.3 The GTAC guidelines were published in September 1994.* They emphasise the key aspects of information, common to all areas of gene therapy research, which are essential to allow the Committee to make an assessment of the ethical acceptability of the protocol taking into account its scientific merit and the potential benefits. These encompass a justification of the proposed research and its scientific validity, with particular emphasis on whether the clinical course of the disease is sufficiently understood for the outcomes of the trial to be assessable; assessments of the risks of harm and potential benefits, paying attention to the degree of preclinical testing in appropriate models to address questions of efficacy and safety; the eligibility criteria used in the selection of trial participants; the means of informing potential subjects, and obtaining appropriate consent, taking into account the different levels of explanation and detail that individuals will require to come to a sufficient understanding of the research and its significance for them personally; and the arrangements for the long term follow-up of research participants.

4.4 The Committee's approach to the review of protocols is intended to be both detailed and challenging. This is essential if confidence in the system of review is to be maintained. But the Committee also has no wish to place unnecessary hurdles in front of investigators. The review process is designed to be enabling, to permit sound research to proceed, and to move towards therapeutic application.

* GTAC "Guidance on making proposals to conduct gene therapy research on human subjects" is available from the GTAC Secretariat (address on inside front cover).

SECTION 5 - FUTURE WORK

5.1 In March of this year, the US Government's RAC agreed a list of types of protocol that would be cleared by "streamlined" or accelerated review without going to the full Committee. This approach has been further developed after discussions between the Food and Drug Administration and the National Institutes of Health so that it is now proposed that RAC will only review routinely the novel aspects of gene therapy research - such as new delivery systems, application to new diseases etc.

5.2 The approach of carrying out a less intense review of the familiar is well established in many areas of emerging technology. During 1993 and 1994 we have seen this applied to the field release of genetically modified crops in the US and UK. It is reasonable to expect that as experience grows, GTAC may develop similar accelerated review of well tried approaches to gene therapy research. However, we must recognise at this time only twelve trials have been submitted in the UK, covering seven diseases and three different approaches to gene delivery.

5.3 GTAC expects to see an increase both in the number and range of proposals requiring review. It will be in the light of such change that GTAC may wish to reexamine its system of review and make appropriate recommendations to Ministers.

5.4 GTAC also expects to keep the field of gene therapy internationally under review including the methods of dissemination of information to the public.

SECTION 6 - REFERENCES

1 **US National Institutes of Health.** "Points to consider in the Design and Submission of Human somatic Cell Gene Therapy protocols". Federal Register 1989, 54: 36698-36703.

2 **Department of Health.** Report of the Committee on the Ethics of Gene Therapy. London HMSO, 1992; Cm 1788.

3 **Caplan NJ, et al.** Liposome-mediated CFTR gene transfer to the nasal epithelium of patients with cystic fibrosis. Nature Medicine 1995; 1: 39-46.

4 **French Anderson W.** Editorial. Human Gene Therapy 1993; 4: 701-702.

5 **Grossman M et al.** Successful ex vivo gene therapy directed to liver in a patient with familial hypercholesterolaemia. Nature Genetics 1994; 6: 335-341.

6 **Office of Recombinant DNA Activities.** ORDA Report: Human gene marker/therapy clinical protocols. Human Gene Therapy 1994; 5: 553-563.

SECTION 7 - GLOSSARY

ADA deficiency

In many inherited genetic diseases, a *gene* is missing. The lack of the normal gene product, in this case the *enzyme* adenosine deaminase, can cause *cells* to function incorrectly and die.

B cell

The type of *lymphocyte* that secretes antibodies.

B.Galactosidase (B-Gal)

An *enzyme* found in the common gut bacterium, E coli which is used as a label for showing that a gene has been successfully transferred into a new *cell*.

Body cell (somatic cell)

Any *cell* of the body except a *germ line cell*. Changes in body cells, notably changes in their genetic make-up, affect only the individual who possesses them, not individuals of succeeding generations.

Cationic liposome (see *liposome*)

Cell (see also: *body cell, germ line cell, somatic cell*)

The smallest unit of living organisms which, given the right conditions, can survive independently and reproduce itself. It has been estimated that the body of a human adult comprises 50 million million cells.

Chromosomes

Microscopically characteristic bundles which carry the *DNA* contained in the nucleus of a *cell*, and the vehicles in which the DNA is carried during reproduction. Each chromosome contains a very long double strand of DNA, bearing thousands of *genes* in a linear array. Chromosomes are present in pairs, in *body cells*, but only one of each pair is present in *gametes*. In human beings there are normally 46 chromosomes. 44 are arranged, and numbered in order of decreasing size, as 22 matching pairs. The two remaining chromosomes are sex chromosomes, in females XX and in males XY.

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

The *protein* plays an important role in controlling the passage of salts out of cells. In cystic fibrosis the *gene* controlling this protein (the CFTR gene) is faulty.

Cytokines

Proteins which help control the behaviour of white blood *cells*.

DNA (deoxyribonucleic acid)

The chemical substance of which a gene is made and which encodes genetic information.

Enzyme

A *protein* which catalyses one of the body's many chemical reactions, which together constitute metabolism - the processes that enable continued functioning and growth. A deficit in the production of an enzyme or its working may result in an inherited disorder of metabolism.

Express (see *gene expression*)

Gamete (see also: *chromosomes*)

A reproductive *cell*: sperm in males, ovum in females. It carries inherited characteristics from parent to offspring.

Gene

A sequence of *DNA* which codes for one *protein* and which may be responsible for an inherited character difference.

Gene expression

The production by a *cell* of the *protein* for which the specific gene codes.

Genetic diseases or disorders

Afflictions which are the result of defects in the

genetic endowment of an individual. They may be the direct consequences of defects in single *genes*; or in whole *chromosomes*, parts of which may be lost, duplicated or misplaced; or from the interaction of multiple genes and external factors in fetal development. Later in life such interactions seem to be the basis of many of the common serious disorders, such as heart disease, diabetes, and cancer, although these are not usually thought of as genetic disorders.

Gene therapy

Used without qualification means the genetic modification of *body cells* of an individual patient, directed to alleviating disease in that patient.

Germ line cells

Those *cells* which are set apart early in embryonic life to become *gametes*, cells of reproduction; sperm in males, ova in females.

Immunoglobulin

A *protein* which has antibody activity.

Liposome

Fatty droplets, liposomes containing *DNA* which can cross into a cell carrying the *genes* needed for *gene therapy*.

Lymphocyte

A type of white blood *cell*, important in immunity.

Metastatic

Disease, usually cancer, that has spread from one site to another unconnected organ.

Molecular biology

The study of *proteins* and *nucleic acids*, substances that make up the living world, their structures and their relationship to biochemical activity; and the substances that are the repositories of genetic information and the agencies for its communication from one generation to the next.

Mutation

A molecular event in which *DNA* is altered with genetic consequences. A *gene* which has undergone mutation is called a mutant; so also is an organism in which the mutant gene is *expressed*.

Nucleic acid

DNA is a type of nucleic acid. A second type of nucleic acid is called RNA which is the genetic material of some *viruses* such as *retroviruses*.

Neomycin (neo)

The *gene* coding for resistance to the antibiotic neomycin may be used as a label in gene transfer (*see also: B-Gal*).

Plasmid

A circular structure of *DNA* usually of bacterial origin, which in nature transfers genes from one bacterium to another. Plasmids are used in some gene therapy trials in place of *virus vectors*.

Promoter

A short piece of *DNA* which controls the *expression* of other *genes*. Changing the promoter may alter the behaviour of genes.

Protein

Proteins are essential constituents of the body. They form the structural materials of muscles, tissues, organs, and are regulators of function, as *enzymes* and some hormones. Proteins are coded for by *DNA*.

Purging, purging techniques

In bone marrow transplantation it may be important to remove any harmful *cells* from the marrow before it is returned to the patient. This process is called "purging".

Retrovirus

A type of *virus* used in *gene therapy* as a *vector*. Such viruses are usually animal viruses rather than agents of human disease. They are made safe so that they can enter a human cell carrying a gene for gene therapy without causing disease.

Somatic cell (see *body cell*)

Stem cell

A *cell* that throughout life is able to produce all the cells within an organ. A change, whether accidental or engineered, in the genetic complement of a stem cell will be passed to its progeny, and may be expressed in them. Appropriate stem cells are therefore an obvious target in somatic cell *gene therapy*.

Vectors

In most situations, a new *gene* cannot be added to human cells without being transported into the cell in some form of a carrier - usually a *virus*, a *liposome* or a *plasmid*.

Virus

A tiny infectious organism, able to reproduce only within a host *cell*. Viruses carry *nucleic acid* surrounded by *protein*. Some cause disease, eg chicken pox, influenza. Some viruses, however, suitably modified, can be used in research as a means of delivering a *gene* into cells.

ANNEX 1 - TERMS OF REFERENCE OF GTAC

The terms of reference of the Gene Therapy Advisory Committee (GTAC) are:

(1) To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks.

(2) To work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities - the Medicines Control Agency, the Health and Safety Executive, and the Department of the Environment.

(3) To provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee will have a responsibility for:

(a) Providing advice for applicants on:

(i) the content of proposals, including the details of protocols, for gene therapy research on human subjects;

(ii) the design and conduct of the research;

(iii) the facilities necessary for the proper conduct of the research;

(iv) the arrangements necessary for long term surveillance and follow up.

(b) Receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

(i) the clinical status of the subjects;

(ii) the scientific quality of the proposal;

(iii) the scientific requirements and technical competence necessary, for carrying out gene therapy research effectively and safely;

(iv) whether the clinical course of the particular disorder is known sufficiently well for

• sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject)

• the outcomes of therapy to be assessable;

(v) the potential benefits and risks for the subject of what is proposed.

ANNEX 2 - MEMBERSHIP OF GTAC

Chairman

Professor Dame June Lloyd, DBE MD FRCP
formerly Professor of Child Health
Institute of Child Health, London

Members

Dr Elizabeth Anionwu, PhD, RGN, HV Tutor
Mothercare Unit of Clinical Genetics and Fetal Medicine
Institute of Child Health, London

Mrs Rosemary Barnes
Director, WellBeing - The health research charity for woman and babies,
London

Professor Martin Bobrow, CBE, DSc, MB, BCh, FRCP, FRCPath
Paediatric Research Unit
United Medical and Dental School, London

Professor Derek Crowther, PhD, MB, BChir, MA, MSc, FRCP, FRCR
Christie CRC Research Centre
CRC Department of Medical Oncology
University of Manchester

Professor Anthony Dayan, MD, FRCP, FRCPath, FFPM, FIBiol
Director
Department of Toxicology
St Bartholomew's Hospital, London

The Rev. Canon Dr Keith Denison, MA, PhD.
The Church in Wales
Diocese of Monmouth

Dr Brenda Gibson, FRCP, FRCPath, DFM
Department of Haematology
Royal Hospital for Sick Children, Glasgow

Mrs Rosemary M Knights, RGN, OND, DN
Chief Executive
Warrington NHS Trust Hospital, Cheshire

Professor Peter Lachmann, ScD, FRCP, FRCPath, FRS
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Medical Research Council Centre, Cambridge

Dr Theresa Marteau, MSc, PhD, CPsychol
Psychology and Genetics Research Group
United Medical and Dental School, London

Professor Norman Nevin, BSc, MD, FRCP, FRCPath
Northern Ireland Genetics Services
Department of Medical Genetics
The Queen's University, Belfast

Miss Eleanor F Platt QC
The Temple, London

Dr Brian Richards, CBE, BSc, PhD
Executive Chairman,
Peptide Therapeutics
Group PLC
Cambridge

Mr Nick Ross
Broadcaster and journalist, London

Professor C Michael Steel, MB, ChB, PhD, DSc, FRCPEd, MRCPath
School of Biological and Medical Sciences,
University of St Andrews, Fife.

Professor Robin Weiss, PhD, FRCPath, Hon. MRCP
Institute of Cancer Research
Chester Beatty Laboratories, London

Observers:

Dr Ian Lister Cheese, PhD, FRCP
Department of Health, London

Dr Brian Davis, MRCP
Medicines Control Agency, London

Secretariat:

Mr Anthony J Taylor, MSc, MIOSH
Ms Jill Elliott

ANNEX 3 - EXPERT ADVISERS TO GTAC

During the period of this first report, GTAC sought the views of the following expert advisers during the review of protocols submitted to the Committee.

Professor Judith Chessells, Institute of Child Health, London

Professor Alan Craft, Royal Victoria Infirmary, Newcastle Upon Tyne

Professor Kay Davies, University of Oxford

Professor John Dodge, Queen's University of Belfast

Professor Tim Eden, St Bartholomew's Hospital, London

Professor John Goldman, Royal Postgraduate Medical School, London

Professor Frank Grosveld, Erasmus Universiteit, Rotterdam

Professor David Linch, University College and Middlesex School of Medicine, London

Professor James Neil, University of Glasgow Veterinary School

Dr Peter Rigby, National Institute for Medical Research, London

Professor Anthony Segal, Raine Institute, University College, London

ANNEX 4 - OTHER BODIES WITH RESPONSIBILITIES IN GENE THERAPY RESEARCH

Although all proposals for gene therapy research should be submitted for review by GTAC and the LREC, other bodies have interests and responsibilities in relation to gene therapy research, among them statutory responsibilities, of which applicants should be aware.

Medicines Control Agency

The Medicines Control Agency (MCA) has responsibility for regulating the handling and preparation of medicinal products, and applications for their use in clinical trials. This responsibility derives from the provisions of the Medicines Act 1968 and Directive 65/65/EEC as modified by subsequent legislation. Proposals for gene therapy research will come within the scope of requirements applying to clinical trials, and subsequent consideration of any application for a product licence. **Any proposal to conduct gene therapy research should, therefore, be notified to MCA.**

Health and Safety Executive

The Health and Safety Executive (HSE) was established under the Health and Safety at Work etc Act, 1974 (HSWA). It is primarily concerned with the protection of human health from possible ill-effects of any workplace activity. Genetic modification and any activities in which genetically modified cells or organisms are cultured, stored, used, transported, destroyed or disposed of, under conditions of containment, are subject to the control of HSE under the Genetically Modified Organisms (Contained Use) Regulations 1992, which are made under HSWA.

In Northern Ireland, contained use matters are covered by the Genetically Modified Organisms (Contained Use) Regulations (Northern Ireland) 1994 and are the enforcement responsibility of the Department of Economic Development.

Department of the Environment

In Great Britain, research in which viable genetically modified cells or organisms may be spread into the environment (for example as a consequence of the use of viable viral vectors) may require the consent of the Department of the Environment (DoE) under the provisions of the Genetically Modified Organisms (Deliberate Release) Regulations 1992.

Northern Ireland legislation for deliberate release is the responsibility of the Department of Environment for Northern Ireland.

National Health Service

Responsibility for deciding whether a research proposal should proceed within the National Health Service (NHS) lies with the NHS body within whose sphere of responsibility the research would take place. NHS bodies are asked to ensure that the proposal has been submitted to the appropriate LREC for ethical approval. The LREC must be consulted about any research proposal involving NHS or NHS Trust patients, premises or facilities.

Medical Research Council

The Medical Research Council (MRC) is the major Government source of funding for biomedical research, and has recently (1993) received additional resources for an initiative on the Genetic Approach to Human Health (GAHH). A steering committee has been set up to oversee the initiative, to channel genetics research towards the improvement of human health and to advise on priorities for investment. Many of the proposals submitted to GTAC will be funded as a consequence of this initiative, having first been assessed by peer review.

Other funding bodies

Charitable bodies make a major contribution to funding research in human gene therapy. To ensure that their interests and close involvement are taken fully into account, they are represented in the advisory mechanism set up within the GAHH initiative to advise the MRC and UK Health Departments.

ANNEX 5 - GENE THERAPY RESEARCH (1993/94)

#	Details	Centre	Outline Approval	Trial Commenced	Report back	Vector/gene	Packaging cell line
001	SCID-ADA	Institute of Child Health/ Great Ormond Street Hosp	1-93	3-93	11-93	ADA	Ψ-CRIP/GP+ env AM12
002	CF Nasal trial	Royal Brompton	3-93	9-93	6-94	Liposome DC-Chol/CFTR	–
003	B-cell lymphoma	MRC Cambridge	7-93	11-94	–	pVAC1/anti idiotype immunoglobulin	–
004	Neuroblastoma	ICRF Bristol	2-94	–	–	LNL-6/neo GIN-neo	PA317
005	Metastatic melanoma	ICRF Oxford	5-94	10-94	–	pNASSB-BGal pNASSB-IL2	–
006	Metastatic melanoma	Institute of Cancer Research/ Royal Marsden Hosp	2-94	–	–	MFG-S-IL2	Ψ-CRIP
007	CF Nasal trial	Oxford/Cambridge	2-94	–	–	Liposome DC-Chol/CFTR	–
008	CF Nasal trial	Edinburgh	5-94	–	–	Liposome DOTAP-CFTR	–
009	CF lung trial	Royal Brompton Hosp	9-94	–	–	Liposome DC-Chol/CFTR	–
010	Lymphoma	University College London Medical School	12-94	–	–	pHaMDR-1	GP+env AM12

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